IMPROVING HUMAN NUTRITION FOR OPTIMAL HEALTH

Panel Manager - Dr. Sung I. Koo, Kansas State University
Program Director - Dr. Etta Saltos

This program area emphasizes research that contributes to our understanding of appropriate dietary practices throughout the life cycle and factors that affect these requirements such as gender, race and ethnicity. In addition, new insights are needed about factors that affect the attitudes and behavior of consumers toward food. The following areas of research will be emphasized: nutritional requirements including metabolism and utilization for all age groups, bioavailability of dietary components, the interrelationships among dietary components, mechanisms underlying the relationship between diet and optimal health (such as the effect of nutrients on the immune system) and cellular and molecular mechanisms influencing nutritional status (including nutrient effects on gene expression). In addition, this program supports research on identification of obstacles to adopting healthful food habits with particular emphasis on factors affecting consumer attitudes and behavior and development of recommendations for interventions to improve nutritional status. Innovative approaches to these research problems are encouraged.

2000-01035 Variations of Biotin Metabolism During the Cell Cycle
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Strengthening Award; Grant 01- 35200-10187; $175,000; 2 Years

Little is known about the nutritional requirement for the vitamin biotin, but recent studies indicate that mild biotin deficiency occurs commonly in pregnancy, raising concerns that the deficiency leads to birth defects. To better understand the mechanisms generating and meeting the requirements of growing cells (such as those of a fetus), the investigators will study the molecule responsible for biotin transport into human lymphocytes. Lymphocytes are an appropriate model because they can be stimulated to divide rapidly, are readily available in blood, and can be studied in vitro. Stimulated lymphocytes increase biotin uptake by about 500% per cell. The investigators will test the hypothesis that increased transport occurs at specific phases of the cell division cycle and results from increased synthesis of the biotin transporter. Further, the transporter synthesis is mediated by increased expression of the gene that encodes the transporter. In lymphocytes stopped at various stages of the cell, both transporter activity and gene expression will be measured. Transporter activity will be measured by uptake of biotin tagged with the radioactive tracer tritium. Gene expression will be measured using cDNA probes for the transporter gene. A better understanding of what constitutes optimal biotin nutrition for individuals including pregnant women, infants, and children will follow from enhanced knowledge of biotin nutrition at the cellular level. The resultant knowledge concerning adequate intakes for optimal biotin nutrition will be useful in choices concerning the growing and selection of foods that meet these requirements.

2000-01068 FASEB Summer Research Conference on Retinoids
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Grant 00-35200-9075; $7,500; 6 Months

This grant will partially support the tenth biannual FASEB Summer Research Conference on Retinoids, scheduled for June 25-30 at the Copper Mountain Conference Center in the year 2000. Vitamin A (naturally occurring retinoids) is an essential animal nutrient obtained only through diet, either as retinyl palmitate from meats or as precursor coratenoids from vegetables. Reproduction (spermatogenesis, placentation, conception, embryonic development), growth, vision, normal metabolism and resistance to infection all require optimal vitamin A in the diet. Our understanding of the impact of vitamin A on

vertebrates is expanding as new research provides novel insight into the diverse and complicated cellular processes that require vitamin A to function. Yet, much of the world's population, especially in Africa and Southeast Asia, lack adequate dietary vitamin A. In addition, economically disadvantaged populations in other areas also suffer from inadequate vitamin A. Therefore, one goal of vitamin A research is to find ways to augment human and animal diets with vitamin A, by direct addition or by growing crops with enhanced vitamin A content, and to understand the impact and required levels of augmentation. Other issues include the impact of inadequate, normal and excess vitamin A on health and the courses of diseases, the mechanisms through which vitamin A on health and understanding the spectrum of vitamin A's effects. This FASEB conference provides the home base for a rapidly growing and diversifying international school of scientists who work with vitamin A.

2000-01036 Holotranscobalamin II: a Non-isotopic Test for Vitamin B_{12} Absorption

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Grant 00-35200-9073; $175,000; 30 Months

The purpose of this research is to develop and validate a new test that can diagnose malabsorption of vitamin B_{12}. About 25% of elderly persons in the US, and a high proportion of individuals of all ages in developing countries, are at high risk of developing vitamin B_{12} deficiency. They cannot absorb the vitamin from food because of a condition called gastric atrophy which causes low stomach acid secretion. Currently vitamin B_{12} absorption is rarely tested, because the only available test (Schilling test) uses radioactivity, and is expensive and impractical. The new test proposes to measure vitamin B_{12} absorption by giving a small oral dose of the vitamin and assessing the subsequent increase in the amount of vitamin B_{12} bound to its binding protein (holotranscobalamin II, or holoTC II) in serum. The test will be developed in young subjects with no vitamin B_{12} absorption problems, testing different doses of both free and food-bound crystalline vitamin B_{12}, and measuring the increase in serum holoTC II from baseline to 6 to 24 hours after the dose. The best protocol that emerges will then be tested in elderly subjects with no B_{12} deficiency; in patients with pernicious anemia who should have minimal B_{12} absorption; in pernicious anemia patients after treatment with intrinsic factor which should improve their absorption; and in suspected B_{12} malabsorbers followed by confirmation of malabsorption with the Schilling test. The new holoTC II absorption test could provide us with a practical way for diagnosing vitamin B_{12} malabsorption in large numbers of individuals of all ages under both clinical and field conditions, and enable us to assess the effects of treatments that could improve absorption.

2000-01049 Neural Responses to Disproportionate Amino Acid Diets: Role of Monoamines

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Grant 00-35200-9069; $150,185; 3 Years

The long-term goals of these studies are to determine the cellular mechanisms by which deficiencies of essential amino acids are detected. The anterior piriform cortex (APC) of the brain is believed to house the essential amino acid sensor. We have shown that the primary event in this recognition is reduced concentration of the most limiting essential amino acid in the APC. The second step of the response is an anorexic response to the diet that caused the deficiency. Our experimental objectives are to determine the effects of the limiting amino acid on brain cells in culture, using electrical recordings from individual cells. Second, to determine the cellular signals underlying these responses in APC tissue, we will use a brain slice preparation exposed to experimental amino acid mixtures and agents. This will allow us to demonstrate the signaling pathways that are activated in the brain cells in place in the tissue. Finally, we will use the successful agents determined in the first two studies to verify the results in the whole behaving animal. The appropriate essential amino acid and/or agent will be microinjected into the APC and the feeding behavior of the animals will be recorded. These studies will provide valuable information about the importance of selecting balanced amino acid profiles for a nutritious diet and contribute to the goal of optimal human health.

Also, this work can provide the basis for future treatment of anorexia, as well as interventions in food faddism, counter-productive food selection and inappropriate supplementation.

2000-01182 Alternative Strategies of Nutrition Education for Low-Income Hispanics (Interactive Multimedia)

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Grant 00-35200-9114; $230,000; 3 Years

Nutrition education programs play a critical role in improving diet and optimal health. Hispanics as a whole face nutritional and health concerns unique to their genetic admixture, culture, and overall population. This project will enhance the development of a bilingual nutrition education program using computer technology to educate low-income, Hispanic, and migrant workers regardless of literacy level. Interactive multi-media also acts as a reliable, cost-effective, and "customized" educational tool with endless possibilities for nutrition education with this population. Concurrently, outcomes in the form of knowledge, skills, attitudes, and behavior will be assessed in a non-invasive manner using computer technology. Objectives include: 1) to improve the existing bilingual interactive multimedia nutrition education program; 2) to develop a 24 hour food recall tool that can be incorporated into interactive multimedia used in community-based interventions; and 3) to adapt a current data management system that will measure outcomes to determine knowledge, attitude, and behavioral impacts and that will accommodate the needs of nutrition assistance programs.

2000-01171 Effects of Zinc on Nuclear Actions of Thyroid Hormone

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Strengthening Grant; Grant 01-35200-9855; $135,000; 2 Years

Both zinc and thyroid hormone are known to play critical roles in support of the growth and development of humans and other animals, though the exact mechanisms are unclear. The possibility of an interaction between their effects exists because zinc is thought to be important for the structure and function of the thyroid hormone receptor, a key protein that mediates the actions of thyroid hormone in the nucleus. However, we have shown previously that removal of zinc enhances the induction of growth hormone gene expression by thyroid hormone in rat pituitary tumor cells. The aim of this proposal is to determine whether other thyroid hormone target genes in other cell types respond in this unexpected way to lack of zinc and to investigate the mechanisms underlying these effects. Primary cultures of rat pituitary and liver cells will be prepared and the effects of zinc removal on thyroid hormone induction of well-characterized target genes within these cells tested. The effects of zinc removal on other agents that activate expression of these genes will also be checked. Experiments with pituitary tumor cells will be repeated using alternate methods to lower cellular zinc and the movement of zinc out of the cells will be monitored. Regulatory regions of the growth hormone gene will be tested to see which are required to see an effect of zinc removal. These studies should identify nuclear processes particularly sensitive to zinc and therefore help link the molecular and physiological roles of this nutritionally significant mineral.

2000-01271 Energy Requirements for Active Pregnant Women

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Seed Grant; Grant 00-35207-9076; $70,751; 2 Years

The intent of this proposal is to begin to identify changes in energy metabolism that occur during each trimester of pregnancy in both active and non-active women. We believe that mothers for whom pregnancy is a risk period for obesity will show the greatest reliance on carbohydrate as an oxidative source and the greatest gain in body fat content during pregnancy. These mothers most likely will not lose all body fat gained

during gestation. Mothers who participate in regular physical activity during pregnancy will primarily utilize fat as a fuel more effectively than sedentary mothers both at rest and during physical activity. A secondary aim is to gain preliminary data on body weight and physical outcomes in the infants born to both active and non-active women. Maternal activity status may positively impact the eventual body composition of the infant. We will recruit both active and sedentary pregnant women. All subjects will undergo evaluation of energy expenditure and fuel utilization both at rest and during physical activity, body composition, and daily physical activity during each of the three trimesters. Additionally, the subjects will have body composition analyzed during the initial postpartum period. We will attempt to identify the impact of activity on physical and physiological changes in the mother throughout pregnancy. The active women should have higher fat utilization and decreased fat storage compared to the sedentary women. Furthermore, the infants from the active mothers will have reduced body fat.

2000-01094 Dietary Protein Affects Calcium and Bone Metabolism

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Grant 00-35200-4420; $140,000; 3 Years

Osteoporosis is a serious disorder affecting millions of Americans. Despite this, we know very little about how nutrients affect bone health. In previous work, we have observed that modest dietary protein restriction in adult women impairs intestinal calcium absorption and leads to an abnormal rise in parathyriod hormone secretion, so called secondary hyperparathyroidism. Further, we have found that when women consume 800 mg/d of calcium and the Recommended Dietary Allowance (RDA) for protein they develop secondary hyperparathyroidism. Since these findings were published, the RDA for calcium has increased from 800 mg to 1,000 mg in young women. These results have led us to formulate the following two specific aims for the current proposal: 1) We will feed women graded levels of calcium while they consume the RDA for protein (0.8 g protein/kg) to determine the optimal level of calcium required at this level of protein intake; 2) We will directly compare the effects of omnivore to vegan protein sources on calcium and bone metabolism in women. The experimental diets used in our previous studies contained both animal and vegetable proteins. Will the same changes observed with these mixed protein sources occur when vegetable/soy is the sole source of dietary protein? These studies will refine current recommendations about appropriate levels of dietary protein and calcium intake as well as sources of protein needed to ensure bone health.

2000-01009 Folate Requirements of Nonpregnant Women by MTHFR Genotype

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Grant 00-35200-9102; $195,000; 3 Years

Folate is a water-soluble vitamin used to make new cells, and to form new chemical compounds required for normal cell function. The body is unable to make folate and depends on adequate dietary intake to keep the body healthy. Folate is concentrated in major U.S. agricultural commodities including orange juice and dark green leafy vegetables. When dietary folate intake is inadequate, a large number of health problems associated with abnormal cell division and function may occur, including anemia, impaired growth, and birth defects. In a significant percentage of the US population (12%), a genetic mutation occurs resulting in a change in one of the major enzyme proteins (methyltetrahydrofolate reductase or MTHFR) required to convert folate to the form most frequently used. The genetic defect causes this enzyme to be less active in affected individuals resulting in lower blood levels of folate and abnormal changes such as elevations in the amino acid homocysteine. This study is the first to address the question of whether women of reproductive age with this genetic defect require a higher dietary intake of folate. The MTHFR genotype of nonpregnant women (20-30y) (n=20) will be determined and changes in folate status response to controlled folate intake will be compared between genotypes. All women will eat a low-folate diet (120 micrograms/day) for 7 weeks followed by an adequate folate intake (600 micrograms/day Dietary Folate Equivalents) for 7 weeks. The study will provide data related to the effect of the MTHFR mutation on folate requirements of women of

reproductive age.

2000-01013 Vitamin B6 Dependence of Homocysteine Metabolism

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Grant 00-35200-9113; $320,000; 3 Years

Adequate vitamin B_6 nutrition is essential for optimal health, and poor vitamin B_6 status is associated with increased risk of cardiovascular disease. Homocysteine is an amino acid that, when present at mildly elevated concentration in blood, is a marker for increased risk of cardiovascular disease and other circulatory disorders. While vitamin B_6 and several other vitamins are involved in controlling the level of homocysteine in the blood, little is known regarding the specific mechanism by which vitamin B_6 deficiency alters homocysteine metabolism. In addition, the intake of vitamin B_6 needed to optimize homocysteine metabolism is not known. These studies involve the use of non-radioactive (stable) isotopic tracers to determine the functional effects of marginal deficiency of vitamin B_6 on the primary pathways governing homocysteine levels in normal human subjects and rats. The administration of stable isotope labeled forms of the amino acids serine, methionine and leucine in a controlled protocol will be used to measure the rates of reactions involved in the formation and disappearance of homocysteine in humans and rats. Healthy adult men and women (5 each) will be evaluated by administration of these tracers while in adequate vitamin B_6 status and following dietary depletion to induce low vitamin B_6 status. Concurrent studies with growing rats fed diets varying in vitamin B_6 will allow assessment of the vitamin B_6 dose-response relationships of these metabolic processes. These studies will expand our understanding of the functional consequences of vitamin B_6 inadequacy and will yield important new information regarding nutritional effects on homocysteine metabolism.

2000-01327 Vitamin B_{12} Deficiency in Elderly Nutrition Programs

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Grant 00-35200-9103; $200,000; 2 Years

The Administration on Aging's Elderly Nutrition Program provides meals for over 3 million older adults each day. We recently reported that more than 25% of these elders have vitamin B_{12} deficiency. Vitamin B_{12} deficiency is linked to high homocysteine (a risk factor for cardiovascular disease), neurological disorders, cognitive problems, cancer, impaired immunity, and hearing loss. Thus, vitamin B_{12} supplements may improve health and lower health care costs in older adults at high risk for vitamin B_{12} deficiency. Our objectives are to determine the prevalence and risk factors for vitamin B_{12} deficiency, relationships of vitamin B_{12} deficiency with other health problems, and the health benefits of vitamin B_{12} supplements in older adults in Elderly Nutrition Programs. The expected outcomes are that vitamin B_{12} deficiency will be associated with low intakes of meat, poultry, fish, dairy foods, fortified foods and nutritional supplements, and linked to several health problems such as high blood homocysteine, poor hearing and poor cognition. It is also expected that vitamin B_{12} supplements will lower blood homocysteine (thus decreasing the risk for heart disease), and will improve hearing and cognition in these elders. Results will provide a scientific basis for recommending a specific amount of vitamin B_{12} for this vulnerable population as a dietary supplement or in fortified foods that can be incorporated into Elderly Nutrition Programs. This research is significant to U.S. agriculture because it will identify dietary risk factors for vitamin B_{12} deficiency, and provide a rationale for development of fortified foods for this public assistance program.

2000-01008 Impact of Dietary Fat Composition on Intestinal Function of Neonates

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Grant 00-35200-9104; $120,000; 2 Years

Premature delivery and low birth weight in the U.S. have risen in the past two decades. Immature gastrointestinal function and their likelihood of developing necrotizing enterocolitis (NEC) places these infants at risk. NEC occurs in 15% of infants less than 3.3 pounds at birth and 40% of infants who develop NEC die. Formulas for premature infants contain fat sources not found in formulas for term infants. For example, medium chain fatty acids (MCT) are currently added to premature infant formulas. In addition, whether to add long chain polyunsaturated fatty acids (LCPUFA), specifically arachidonic acid (AA) and docosahexaenoic acid (DHA), to premature infant formulas is under debate as these fatty acids have been shown to beneficially impact brain and retinal development of premature infants. The *objective of this application* is to determine how MCT and LCPUFA added to infant formula impact upon intestinal digestive function and immune cell composition and function. These studies will utilize the neonatal piglet as an animal model and will compare the experimental formulas to formulas containing the blend of fats present in term infant formulas. We are particularly interested in intestinal immune function as preliminary studies in premature infants has shown that dietary LCPUFA reduced the incidence of NEC. The proposed research will investigate the relationship between diet and intestinal health and diet and intestinal gene expression in neonates. Determining the impact of dietary fat composition on intestinal digestive and immune function will allow for the optimization of nutrition support practices for premature infants.

2000-01024 Carotenoid Bioavailability and Metabolism

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Grant 00-35200-9074; $145,000; 3 Years

Provitamin A carotenoids are the major source of vitamin A for most humans on earth. Uncertainty exists about the nutritional value of these carotenoids relative to vitamin A. Public health strategies for improving the vitamin A status of children and pregnant women worldwide are consequently influenced. For example, should continued stress be placed on the eating of fruits and vegetables as sources of vitamin A, or should the major focus shift to the ingestion of animal foods that contain preformed vitamin A. Such decisions can affect the health and development of hundreds of millions of individuals in high-risk groups. The objectives of the current grant are to evaluate the validity of three unverified assumptions about the nutritional value of ingested provitamin A carotenoids, namely that nonabsorbed carotenoids are destroyed to a significant extent in the large bowel. Absorbed beta-carotene that is not immediately converted to vitamin A is of minor nutritional significance, and the extent of beta-carotene conversion to vitamin A is largely dependent on the vitamin A status of the individual. These assumptions will be tested by studies in the white rat, which has proven to be a good model for most metabolic transformations of carotenoids and vitamin A in humans. The results of the studies should reduce the uncertainty about the nutritional value of ingested provitamin A carotenoids in humans. This project fits well with an essential aspect of the agricultural enterprise in the United States, namely, the effective use of foods to maintain good health.

2000-01321 Folate-Retinoid Interactions: Implications in Liver Disease

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New Investigator Award; Grant 01-35200-09854; $181,967; 2 Years

Many nutrients play a significant role in both health and disease. Our long-range goal is to understand how different nutrients interact with each other to influence the development of liver disease so that effective dietary interventions can be designed to prevent their adverse affects. The objective of this research is to identify the mechanism by which vitamin A compounds and derivatives, termed retinoids, cause liver damage. We hypothesize that specific retinoids mediate the abnormal metabolism of the vitamin folate, thereby interfering with normal folate function. Ultimately, this disruption of folate metabolism and function by retinoids results in liver damage, as exemplified by the development of a fatty liver. We will test our hypothesis by examining folate metabolism and function in retinoid-treated rats. Furthermore, we will

examine how dietary protein can exacerbate or prevent the liver damage associated with retinoid administration, depending on its level in the diet. The role of nutrition and nutrient interactions, in particular the interaction between retinoids and folate, can play a significant adverse and beneficial role in the development of liver disease. The rationale and significance of this research is that understanding these interactions will provide a basis for establishing dietary recommendations directed at minimizing or preventing the development of liver damage that can lead to more chronic disease states. Moreover, retinoids are used clinically for their therapeutic value even though they exhibit numerous side effects. Thus, this research will aid in the evaluation of existing and new retinoid compounds in efforts to minimize their toxicity.

2000-01328 Dietary Fatty Acid-Induced Oxidative and Inflammatory Environments in Endothelial Cells

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Strengthening Award; Grant 00-35200-9101; $171,000; 3 Years

Atherosclerosis leading to heart disease or stroke is the major cause of death in the United States. Mechanisms of the development of atherosclerosis are not fully understood. However, inflammatory reactions within the vascular wall can play a critical role in this disease through induction of injury to endothelial cells. Normally, endothelial cells, which form the lining of the blood vessels, protect the vessels against atherosclerosis. However, when injured or activated, endothelial cells lose their ability to create a barrier to blood-borne injury factors. Consequently, lipids, including cholesterol, may accumulate within the vessel wall and form atherosclerotic plaques. The current proposal is part of our ongoing research on mechanisms of fatty acid-induced injury to endothelial cells in relation to the development of atherosclerosis. We hypothesize that specific dietary fatty acids can induce oxidative stress and inflammatory reactions within the vascular endothelium. Our study will involve analysis of expression of the genes which control and participate in the development of inflammatory responses. In addition, we will use state-of-the-art techniques to assess cellular oxidative stress. The long term goals of the present proposal are to determine molecular mechanisms of endothelial cell dysfunction induced by dietary fatty acids. We also will explore potential mechanisms by which antioxidant supplementation can prevent induction of endothelial dysfunction. Thus, the current research proposal can significantly contribute to the improvement of public health by providing important research data about the role of dietary factors in the development or prevention of endothelial cell inflammatory response in relationship to atherosclerosis.

2000-01010 Regulation of APO A-I Gene Expression by Phytoestrogens

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Grant 00-35200-9066; $200,000; 2 Years

Apolipoprotein (apo) A-I is the major protein component of high-density lipoproteins (HDL) and is produced by the liver and the intestine. Low plasma levels of both apo A-I and HDL cholesterol are associated with an increased risk of coronary heart disease. In addition, elevated HDL levels have been defined as cardioprotective. Therefore, any factor that has the ability to increase apo A-I and HDL cholesterol levels may protect from heart disease. We have shown that both estrogen and the phytoestrogens genistein and daidzein, found in soybean, increase the production and secretion of apo A-I by liver cells. The region of the apo A-I gene that controls the rate of synthesis of apo A-I (from nucleotide-256 to nucleotide-41) in liver cells, also confers the estrogen and phytoestrogen responsiveness. In this project, we propose: 1) to identify the specific sequence within the -256 to -41 region of the apo A-I gene involved in phytoestrogen responsiveness, and; 2) to identify the mechanism responsible for the increase in apo A-I production by daidzein and genistein by characterizing the protein(s) in the cell nucleus that bind to this region and promote

the activation of apo A-I production. Understanding the molecular mechanism by which phytoestrogens regulate the expression of the apo A-I gene may lead to the development of improved diets with the ability to selectively increase apo A-I levels by increasing its synthesis and secretion by liver cells and therefore lead to better prevention of coronary heart disease.

2000-01053 Investigation of an Age Difference in the Response to Vitamin D Supplementation
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Grant 00-35200-9061; $96,086; 1 Year

The purpose of this study is to explore possible explanations for our previous observation that older men had smaller increases in blood levels of the storage form of vitamin D (25-hydroxyvitamin D) when given vitamin D (cholecalciferol) supplements. Explanations include poorer absorption of vitamin D, delayed or reduced transport through the circulation, reduced metabolism in the liver, and increased breakdown of vitamin D metabolites. These possibilities will be examined by comparing changes in different forms of the vitamin (cholecalciferol, 25-hydroxyvitamin D, 1,25 dihydroxyvitamin D and 24,25 dihydroxyvitamin D) and the relationships of these to each other and to calcium-regulating hormones. Measurements will be made in stored blood samples collected from 56 men, 28 young (18-35 years) and 28 old (62-79 years), who were randomly assigned to 800 IU/d of vitamin D or to a control group, and followed for eight weeks in winter. Four sequential measurements were made in the subjects over the eight-week study, and this will allow us to describe and compare the timing of changes during supplementation. This study will improve our understanding of the metabolism of oral vitamin D in young and older adults, and will provide information relevant to vitamin D intake recommendations. The results will also be relevant to U.S. agriculture because fortified milk is the primary dietary source of vitamin D in the United States.

2000-01314 Function of Vitamin A in Quail Embryogenesis
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Grant 00-35200-9062; $180,000; 3 Years

The long term objective of this research is to understand the physiological function of vitamin A in early embryonic development. Maternal insufficiency of vitamin A during pregnancy causes severe fetal abnormalities; they include abnormalities in the development of the heart, the circulation and the brain. Vitamin A is specifically required in the early stages of heart and blood vessel formation. However, the exact role of vitamin A in early embryonic development is not known. We will use molecular biology and immunological tools to examine the mechanisms of vitamin A function in the cardiovascular development in the early embryo when the presence of vitamin A is critical. We will use an avian model system in which the hen is supplemented with a form of vitamin A that cannot be deposited in the fertilized egg. Thus, we can have a vitamin A-deficient avian embryo in which we can study the role of vitamin A during development by supplementing vitamin A to these deficient embryos and then following their course of development. Without vitamin A these embryos do not live beyond 4 days, but they are useful to study early developmental stages. This is impossible with a mammalian model, since the mother would not survive without vitamin A. The early embryonic development is similar among vertebrates and results from the avian model can be applied to mammals. Data from this research will contribute to the understanding of the critical need for vitamin A for the formation of the heart and circulatory system and will provide a basis for evaluating requirements for vitamin A during embryonic development.

2000-01070 Stages of Change and Fruit and Vegetable Consumption by African American Mothers
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Grant 00-35200-9064; $145,000; 2 Years

There is a consistent relationship between diets high in fruits and vegetables and decreased risk for certain chronic diseases, such as, heart diseases and cancer. Low-income individuals have a disproportionately higher risk for these diseases, yet consume lower levels of fruits and vegetables. The goal of this study is to understand factors predicting fruit and vegetable intake by low-income African American mothers of young children through the application of the Transtheoretical model. This model involves a series of stages of readiness to change eating behaviors, perceptions of benefits (pros) and barriers (cons) to change, and processes used to change behavior. In the first year, information will be gathered by observation and interview as to how decisions are made about incorporating fruits and vegetables into diets for families in the context of where these decisions are made. Verbalizations as part of a "thinking out loud" protocol will be recorded in the grocery store and at home from women in each of the stages of readiness to change intake of fruits or vegetables. Data will be analyzed to identify pros and cons and processes of change used within each stage. In the second year, this information will be used to develop a survey tool to determine how the pros and cons of change and processes of change are related to intake, stage of readiness to change, and provision of fruits and vegetables for children in a larger sample from the target audience. Understanding factors predicting intake and integration into an appropriate theoretical framework is required for effective interventions to increase fruit and vegetable intake in this audience.

2000-01052 Omega-3 Fatty Acids and Th1 Cytokines

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Grant 00-35200-9115; $250,000; 3 Years

Omega-3 fatty acids are essential for the normal development and function of the neonatal brain and retina. However, the consumption of a diet rich in omega-3 fats may impair infectious disease resistance against certain pathogens. Over the past decade our laboratory has demonstrated that high intake of omega-3 fatty acids is associated with impaired bacterial clearance and lower survival in mice that are experimentally infected with a certain type of bacteria (i.e., *Listeria monocytogenes*). We plan to continue to use the mouse to study the impact of dietary omega-3 fatty acids on host infectious disease resistance. Among the things that we hope to determine is whether the early exposure to a diet high in omega-3 fatty acids will have a prolonged impact on the immune response such that protection for re-exposure to the same pathogen is compromised. Other studies will involve using strains of mice with selected gene deletions (i.e., knock-out mice) to clarify which components of the immune response that are affected by omega-3 fatty acids are most important to this impairment in infectious disease resistance. Our long-term goal is to understand the underlying biochemical and molecular mechanism for omega-3 fatty acid actions on the immune response. Such an understanding may allow health professionals to maximize the benefits and reduce the risks associated with eating a diet rich in omega-3 fatty acids.

2000-01227 Promoting Optimal Nutrition Through Assessment of Rural Elderly in Montana

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Seed Grant; Grant 00-35207-9078; $74,309; 2 Years

Rural elderly are especially vulnerable to nutritional problems. However, little is known about their nutritional needs and problems. In Montana 44 out of 56 counties are considered frontier, and travel of long distances is required for food and health services. It is believed that by providing nutritional, health, and social support in the local community, elderly persons will be able to stay in their home longer. This research seeks to improve the understanding of dietary practices of the rural elderly in Montana. Extensive attention will be directed to understanding the physical, social and environmental factors that affect dietary attitudes and behaviors in the rural elderly. This includes extensive dietary and laboratory assessment of both elderly living independently and those receiving home delivered meals in geographically rural settings. The congruence between the rural elder's understanding of nutritional services with the actually availability of

services will be examined. Tying community availability to perceived and actual need in rural Montanans is a different approach to studying nutritional status and is a major strength of this study. By looking at the community itself, obstacles such as distance and availability of services can be identified. Results of this study will provide the basis for the development of new programs and refinement of existing programs to provide interventions aimed at enhancing nutritional status of the rural elderly in Montana.

2000-01093 Fluctuations in Brain Extracellular Glucose Levels: Consequences for Cognitive Functions

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Grant 00-35200-9059; $215,000; 3 Years

Under most circumstances, glucose is the sole source of energy for the brain. The traditional view is that, except under conditions of near-starvation, the amount of glucose in the blood is sufficient to meet the demands of the brain. While this may be the case for basic brain functions, the brain may not always have enough glucose for optimal performance of complex cognitive functions. Evidence that glucose availability may limit some brain functions includes: 1) administration of glucose enhances cognitive functions in humans, rats and mice; 2) extracellular glucose in the brain is present at lower concentrations than previously believed; 3) extracellular glucose in some brain areas is depleted during times of high cognitive load; 4) glucose administration prior to testing enhances cognitive function while preventing the depletion of extracellular glucose in the brain. These findings offer the most direct link currently available between food intake and cognitive functions. The goal of this project is to relate glucose administration to brain and cognitive functions in rats by addressing two main issues: 1) How long before learning can administration of glucose block the depletion of glucose in the brain? Is glucose stored in the brain for later cognitive demands? 2) Is the depletion of glucose specific to those brain areas or general to all brain areas actively engaged by different cognitive tasks? This project will determine several important relationships between glucose and brain functions important for later development of strategies for using nutrition to improve human cognitive functions.

2000-01050 Consumption of Energy-Dense, Nutrient-Poor Foods by American Children

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Grant 00-35200-9067; $130,000; 2 Years

Energy-dense, nutrient-poor foods include fats, oils, and sweets, and are at the tip of the Food Guide Pyramid with recommendation to use sparingly. Recent studies suggest that a greater number of U.S. children are becoming obese. It is speculated that one of the reasons why obesity is increasing in U.S. children may be because they are consuming more energy-dense nutrient-poor foods. However, there has been no comprehensive study of how much of these foods are eaten by children, and how their consumption relates with body weight and overall health of children. The study will use nationally representative data from the third National Health and Nutrition Examination Survey, 1988-1994, for more than 4800 American children and adolescents aged 8-18 years to address these issues. The goals of this proposal are to examine patterns of intake of energy-dense nutrient-poor foods in U.S. children, and the relation of intake of these foods with nutrient intake, compliance with recommendations for a healthy diet, serum levels of vitamins and minerals, and body fatness. The proposed research is important for several reasons. First, knowing about dietary patterns enables us to understand the extent of the problem. Second, knowledge about nutritional or health effects of energy-dense nutrient-poor food intake creates an environment for examining why healthy diet messages are being ignored. Lastly, because dietary habits formed in childhood persist in adult life, it is important to understand diet patterns of children, so that suitable strategies for intervention can be designed and implemented by both the private and public sectors.

2000-01078 Retinoic Acid Signaling

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Grant 00-35200-9065; $400,000; 4 Years

The proposed studies investigate a novel aspect of the mechanism of action of the vitamin A metabolite, retinoic acid, in regulating cell growth and differentiation. Retinoic acid is a dietary factor necessary for proper growth and development in juveniles. It is also a known embryonic morphogen regulating in particular spatial body axis development during embryonic development. Its mechanism of action is thus of interest to improving nutrition and development. It is also an effective potential cancer chemotherapeutic/prevention agent. Retinoic acid is metabolized intracellularly into a variety of retinoid metabolites which activate two classes of proteins, called RAR and RXR transcription factors, that govern gene expression. Since the discovery of RARs and RXRs in 1987, this has become the classical paradigm for the signaling mechanism of retinoic acid. Recently we reported that retinoic acid causes activation of another form of signaling, called MAPK signaling, and that this was necessary for retinoic acid to regulate the growth and differentiation of a human hematopoietic cell *in vitro*. This form of signaling is typically associated with certain growth factors to cause cell division, and it is surprising to find that retinoic acid uses this form of signaling to cause growth arrest and cell differentiation. The proposed studies seek to determine both the upstream events by which the presumed MAPK signaling complex is activated by retinoic acid and the downstream genes regulated by its activation. The results will ultimately contribute to the basic scientific underpinnings that will allow vitamin A to be more effectively used.

2000-01168 Efficacy of Soy Protein in Prevention of Male Osteoporosis

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Postdoctoral Fellowship; Grant 00-35200-9072; $89,997; 2 Years

Osteoporosis is an important yet understudied debilitating disease in men. Male osteoporosis differs from postmenopausal osteoporosis with respect to age of onset. Accelerated bone loss in men occurs around age 65. Among the dietary approaches for improving skeletal health, soy or its isoflavones, a diverse group of compounds that are often referred to as phytoestrogens, have recently received considerable attention. However, in both human and animals, research has focused on female-associated bone loss. Therefore, it is of particular importance to examine the effectiveness of soy or its isoflavones on age-associated bone loss in males. In a dose-response study, we will utilize 105 aged male rats, as a model of male osteoporosis, to determine whether soy protein itself or its isoflavones exert beneficial effects on bone. After 180 days of treatment, effects of soy on bone and calcium metabolism including bone mineral density, bone strength, calcium absorption, and blood and urinary markers of bone formation and bone resorption will be assessed. If the results of the proposed study confirm that soy protein or soy isoflavones preserve or improve bone mineral density and bone quality in old male rats, the findings will have important implications with respect to promoting human nutrition and increasing the demand for soybean production nationwide.

2000-01322 Children's Responsiveness To Increasing Food Portion Sizes

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Grant 00-35200-9063; $85,000; 2 Years

The prevalence of childhood overweight has increased dramatically over the past two decades, highlighting the need to identify environmental factors that increase overweight risk among children. Increasing portion sizes of palatable energy-dense foods are abundant and have been cited as an important factor in promoting overweight and obesity among children. Little is known, however, about how children respond to increasing portion size and the factors that influence children's susceptibility to eat large portions. The objectives of the proposed study are to evaluate the effects of increasing portion size on young children's

understanding of typical portion sizes and food intake patterns, as well as to evaluate individual differences in response to portion size as a function of child age, child and parent weight status, parental eating styles, and child feeding practices. An experimental design will be used to investigate portion size and food intake in a sample of pre-school aged children. We hypothesize that children will increase food intake in response to increased portion sizes. Further, we hypothesize that a greater responsiveness to portion size will be observed among older, heavier children and those children with parents who are heavier, have problems controlling their own eating, and who exercise greater control over child feeding. The findings of this work will identify obstacles to adopting healthful food habits by providing insight on how large portion sizes may contribute to environments and by identifying those children who are most susceptible to this influence.

2000-01029 Enzyme Induction by Dietary Flavonoids: Role in Cancer Prevention

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Strengthening Award; Grant 00-35200-9071; $130,000; 2 Years

Flavonoids are non-essential nutrients found in all plant foods and plant-derived beverages. Population studies have shown that these compounds are protective against various cancers. Our laboratory has found that some of these dietary flavonoids dramatically increase the content of UDP-glucuronosyltransferase (UGT), an enzyme that can inactivate carcinogens in cultured human intestinal cells, and thus protect the cell. Using these human cells, we will determine which particular flavonoids have this inducing effect and which UGT isoforms are induced. We will then test if flavonoid treatment will lead to inactivation of one common human colon carcinogen in these cells. To test to what extent the dietary flavonoids can be absorbed from the digestive tract, they will be administered orally to both rats and humans. In rats, UGT induction will be measured in intestinal preparations and in humans UGT induction will be measured indirectly as increased formation of glucuronides of model substrates in the circulating blood. The overall goal of this project is thus to establish if UGT induction by flavonoids is likely to be a protective mechanism against colon cancer in the general population. Because flavonoids are commonly found in plant foods, such knowledge may help formulating specific dietary recommendations for optimum health. Therefore, the production of plant foods might be modified, specific plants bioengineered to improve their flavonoid composition, and certain foods valued more highly in the marketplace due to their flavonoid composition. The proposed studies may thus provide guidance for sustainable agricultural production that serves human health.

2000-01101 Liquid Chromatograph Mass Spectroscopic Measurement of Folic Acid and Natural Folates in Food

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Seed Grant; Grant 00-35207-9077; $75,000; 2 Years

Current data bases on food folate composition underestimate the true levels of folate in the food supply in view of inadequate extractions employed in previous techniques. The purpose of this grant is to develop robust analytical methods for folic acid and natural folate found in foods using Liquid Chromatograph Mass Spectroscopy techniques.

2000-01312 Enteral Insulin and Intestinal Ontogeny in Preterm Infants

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Grant 00-35200-9060; $300,000; 4 Years

Gastrointestinal (GI) development is underdeveloped in the preterm infant compared with that in the term infant and results in feeding intolerance. Intolerance to feedings adversely affects the health of the

preterm infant resulting in prolonged hospitalization and the need for expensive tests and treatments. Consequently, strategies are needed to enhance GI development in the preterm infant. Human milk contains factors such as insulin that are believed to play an important role in GI development. Administration of insulin in the feeding to the suckling pig and rat has been shown to enhance GI growth and development. Our preliminary data suggest that it does so in the human preterm infant. We hypothesize that the addition of insulin to the feedings of the preterm infant will accelerate GI maturation and thereby decrease feeding intolerance and the cost of care. We will randomize 120 preterm infants to feedings with or without added insulin and compare GI development, feeding intolerance, and the cost of caring for the infants. Using a new and novel strategy, this investigation is likely to improve the health of preterm infants significantly. It will provide insight into the role of biologically active food components in promoting health. These studies also will provide further understanding of the biology of GI development in the preterm infant.

2000-01058 FASEB Summer Research Conference: Folate, B_{12} and One-Carbon Metabolism

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Grant 00-35200-9070; $10,000; 1 Year

This project will provide partial support of the Eighth FASEB Summer Research Conference on Folic Acid, Vitamin B_{12} and One Carbon Metabolism, to be held August 5 - August 10, 2000 at Snowmass Village, Colorado. This conference offers a unique opportunity for clinician scientists, basic scientists, and nutrition scientists from a broad group of disciplines with an interest in folic acid, vitamin B_{12} and one carbon metabolism, to interact both formally and informally. Funds from this project will allow graduate students, residents and postdoctoral fellows, and established national and international scientists to attend the meeting. The program includes well established scientists as well as junior scientists just entering the field. Topics cover the entire spectrum from current human nutrition problems to areas of the most sophisticated biochemical and biophysical research. Sessions have been scheduled on: One carbon metabolism: enzymology and regulation; Homocysteine metabolism and pathophysiology; Methionine metabolism: enzymology and regulation; Methyl group metabolism; Translocation of folate and B_{12} metabolites; Folate-dependent enzyme reactions as targets for chemotherapy; Folates and antifolates in therapeutics; B_{12} Synthesis and B_{12}-dependent Enzymes; Genetic diseases of folate, vitamin B_{12} and homocysteine metabolism. In addition to the formal presentations, the program will be complemented with poster sessions and workshops. The first workshop will update progress of the various homocysteine-lowering vitamin intervention trials for cardiovascular disease prevention. The second will discuss food folate fortification as a public policy. This conference plays a major role in nutrition policy, both in the U.S. and abroad.

2000-01020 The Impact of Interviewer Body Mass Index on Under-Reporting of Energy Intake in Obese Women

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Grant 00-35200-9068; $93,000; 2 Years

Accurate measurements of food intake are essential to determine associations between diet and disease as well as nutrient requirements for optimal health. Unfortunately, data collected from a variety of people demonstrate that under-reporting of food intake is a serious and widespread problem. Women are known to under-report their food intake to a greater extent than men and obese people have been shown to under-report their dietary intake to a greater degree than lean people. The aim of this study is to develop interview methods which improve the accuracy of self-reported food intakes in obese women. It has been shown that the physical characteristics of interviewers can affect the information received during an interview. The specific objective of this study is to determine if obese women provide more accurate reports of their food intake by: 1) telephone interview when the interviewer is unknown to them; 2) by in-person interview with a normal weight interviewer or; 3) by in-person interview with an obese interviewer. One-hundred-ten overweight women

will participate in the study. They will complete a telephone administered multiple-pass 24-hour recall with a previously unknown interviewer. The subjects will then be randomized to two groups of in-person interviews: 1) in-person multiple-pass 24-hour recall with a normal weight interviewer and; 2) in-person multiple-pass 24-hour recall with an obese interviewer. Energy intake will be estimated from the recalls and compared with total energy expenditure to determine reporting accuracy. Results of this study will be used to develop dietary intake methods that minimize under-reporting. This is critical to the integrity of nutrition research as we seek to accurately determine what people are really eating.

2000-01188 Effect of Isomeric Conjugated Linoleic Acid Intake on Milk Fat Content and Growth During the Early Postnatal Period

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Grant 01-35200-09859; $220,011; 2 Years

The term "conjugated linoleic acids" (CLAs) refers to a fats containing 18 carbons and two double bonds separated by one single bond. One form of CLA (rumenic acid; RA) is found in beef and dairy fat. Other forms of CLA are also produced industrially, and may become part of the human food system in the near future. Mixtures of industrially-produced CLAs can inhibit cancer and cause laboratory animals to grow leaner. In the lactating animal, this regimen also decreases milk fat. We do not know which isomers of CLA cause these effects. Thus, we will conduct two sets of experiments to study the potential differential effects of the two major forms of CLA on maternal and infant health. In the first set of studies, breastfeeding women will be asked to consume the two primary CLA isomers so that we can determine which one is responsible for the milk fat depression that we have previously documented. We will then determine whether there is a "safe" level of intake for this isomer. In the next study, lactating rats will be fed diets containing either no added CLA (control) or one of the two major isoforms. Milk composition, pup growth and nutrient partitioning will be monitored. Distribution of these CLAs among various body organs will also be documented. In general, we hypothesize that the naturally-occurring form of CLA will not influence total milk fat or growth of the suckling infant, whereas the industrially-produced CLA will result in milk fat depression and growth faltering.